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ESTIMATION OF LUNG TISSUE DOSES FOLLOWING EXPOSURE TO LOW-LET RADIATION IN THE CANADIAN STUDY OF CANCER FOLLOWING MULTIPLE FLUOROSCOPIES

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ESTIMATION OF LUNG TISSUE DOSES FOLLOWING EXPOSURE TO LOW–LET RADIATION IN THE CANADIAN STUDY OF CANCER FOLLOWING MULTIPLE FLUOROSCOPIES

A report by Geoffrey R. Howe and Martin Yaffe, under contract to the Atomic Energy Control Board.

ABSTRACT

Lung tissue doses from exposure to external low-LET radiation have been estimated for each year between 1930 and 1969 for 92,707 tuberculosis patients first treated in Canadian institutions between 1930 and 1952. A substantial proportion of these patients received multiple chest fluoroscopies in conjunction with treatment by artificial pneumothorax, and thus accumulated lung tissue doses up to 15.7 grays.

The dose estimation model included four components. The radiation output of fluoroscopes in operation during the relevant time period was estimated from published data derived from experimental measurements. Estimates of organ dose per air kerma at the skin entrance were estimated from a combination of previously conducted human phantom experiments together with new Monte Carlo simulations. Data on parameters of exposure such as exposure time were estimated from interviews with 91 physicians who conducted fluoroscopy in Canadian institutions in the 1930s and 1940s. The final component of the dose model was the estimation for each individual patient of the number of fluoroscopies received as a function of calendar year and whether or not the institution in question was in the province of Nova Scotia. The latter distinction is important, since the practice in Nova Scotia was to use anterior-posterior orientation, in contrast with the rest of Canada where this practice was rare.

The integrated complex dose model has been applied to the 92,707 tuberculosis patients for whom data had previously been extracted from sanatoria records, in order to estimate individual lung tissue doses. An evaluation of potential errors in the dose model has been completed. There are a number of sources of such errors, and the most critical one appears most likely to be uncertainty in estimating the average exposure time used for individual fluoroscopic examinations.

The estimated doses have been used in a statistical analysis of lung cancer mortality between 1950 and 1987 occurring among 64,689 patients known to be alive at the start of 1950, and followed by computerized record linkage to the Canadian national mortality data base. There were substantial variations in the total cumulative lung tissue dose received by the cohort members included in the analysis, with 2,490 individuals having doses in excess of 1.7 grays. A total of 1,156 lung cancer deaths was observed in the cohort, and these have been used to estimate relative risks. The most appropriate risk model appears to be a simple linear relative risk function, with an excess relative risk coefficient of 0.089 (95 % confidence interval – 0.057 to 0.175) for an absorbed dose of 1 gray of radiation. This contrasts with estimates of relative

risk based on the atomic bomb survivors study, for which the excess relative risk coefficient for males 20 years after the first exposure is estimated to be 0.64 (95 % confidence interval – 0.07 to 1.21). The difference in effect between the results for the fluoroscopy cohort and the atomic bomb survivors data is statistically significant (p = 0.06). Thus, the difference in effect appears to be unlikely to be due to chance. It is postulated that fractionation and dose rate effectiveness factors may account for some of the discrepancy.

RÉSUMÉ

Les doses aux tissus pulmonaires découlant de l'exposition aux rayonnements externes de faible transfert linéique d'énergie ont été estimées pour chaque année de 1930 à 1969 dans le cas de 92 707 tuberculeux qui ont d'abord été soignés dans des établissements canadiens entre 1930 et 1952. Une grande proportion de ces malades a subi de multiples fluoroscopies pulmonaires pendant qu'ils étaient traités par pneumothorax artificiel, accumulant ainsi des doses aux tissus pulmonaires atteignant jusqu'a 15,7 grays.

Le modèle d'estimation des doses comprenait quatre composantes. Les rayonnements des fluoroscopes utilisés durant la période à l'étude ont été estimés à partir de données publiées et dérivées de mesures d'expériences. Les estimations de la dose à l'organe par kerma de l'air au point d'entrée dans la peau ont été établies d'après une combinaison d'expériences antérieures sur des fantômes humains et de nouvelles simulations de Monte Carlo. Les données sur les paramètres d'exposition, comme la durée d'exposition, ont été estimées à partir de témoignages recueillis auprès de 91 médecins qui se sont servis de fluoroscopies dans des établissements canadiens dans les années trente et quarante. La dernière composante du modèle de dose a été l'estimation pour chaque malade du nombre de fluoroscopies reçues par année civile et l'indication que l'établisse nent en cause était situé en Nouvelle-Écosse ou non. Cette dernière distinction est importante puisqu'il était de pratique courante dans cette province d'utiliser l'orientation antérieure-postérieure, contrairement au reste du Canada où cette pratique était rare.

Le modèle de dose complexe intégré a été appliqué aux 92 707 tuberculeux dont les données avaient d'abord été extraites des dossiers de sanatoriums, en vue d'estimer leur dose individuelle aux tissus pulmonaires. Une évaluation des erreurs possibles du modèle de dose a été exécutée. Ces erreurs sont dues à un certain nombre de sources, dont la plus critique semble être tout probablement l'incertitude qui existe à estimer la période moyenne d'exposition de chaque examen fluoroscopique.

Les doses estimées ont servi à l'analyse statistique des cas de cancer pulmonaire mortel entre 1950 et 1987 parmi les 64 689 malades toujours vivants au début de 1950, puis à des comparaisons informatiques de dossiers avec la banque de données canadienne sur le taux de mortalité national. D'importantes variations sont apparues dans la dose cumulative totale aux tissus pulmonaires reçue par les membres de la cohorte à l'étude, dont 2 490 avaient des doses supérieures à 1,7 gray. On a observé un total de 1156 cas de cancer pulmonaire mortel dans la cohorte et ces cas ont servi à évaluer les risques relatifs. Le meilleur modèle de risque semble être une simple fonction de risque relatif linéaire, comportant un coefficient de risque relatif

excessif de 0,089 (de -0,057 à 0,175, à un intervalle de fiabilité de 95 %) pour une dose absorbée de 1 gray de rayonnement. Ceci ne correspond pas aux estimations de risque relatif de l'étude sur les survivants de la bombe atomique, qui estimait le coefficient de risque relatif excessif des hommes à 0,64 (de 0,07 à 1,21, à un intervalle de fiabilité de 95 %) 20 ans après leur première irradiation. La différence effective entre les résultats de la cohorte des patients de fluoroscopie et les survivants de la bombe atomique est statistiquement importante ($p = 0,06$). Il apparaît donc peu probable que la différence effective soit attribuable au hasard. On postule que les facteurs d'efficacité de fractionnement et de débit de dose pourraient expliquer une partie de l'écart.

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A. INTRODUCTION

1. Exposure to External Low-LET Radiation and Lung Cancer Risk

The study of the survivors of the atomic bombings at Hiroshima and Nagasaki has clearly established that exposure to high levels of external low-LET radiation increases the risk of lung cancer.[1] There is little doubt of the causality of this association, in view of the known carcinogenic effect of low-LET radiation on many body organs, the susceptibility of lung tissue in animal species to radiation induced carcinogenesis, and the clear dose-response relationship seen in the atomic bomb survivors data.[2] However, in order to establish appropriate criteria in terms of lung cancer risk for chronic low dose exposures to external low-LET radiation, it is necessary to extrapolate from the results of high dose studies to the low doses typically encountered in the current occupational or other environments. The primary epidemiologic data for this purpose available to date are those from the atomic bomb survivors study. The latter data were used by the 5th Committee on the Biological Effects of Ionizing Radiation, of the U.S. National Academy of Sciences (the BEIR V Committee)[3] to derive a risk model for lung cancer mortality. This model has the form:

$$r(D) = r_o [1 + (\alpha_1 D)\exp(\beta_1 \ln(t/20) + \beta_2 S)]$$

where r_o = age-specific background risk of death due to lung cancer

D = dose in Gy

t = years since exposure

S = sex, with a value 0 for males, and 1 for females

α_1 = 0.636 (0.291)

β_1 = 1.437 (0.910)

β_2 = 0.711 (0.610)

(standard errors in parentheses)

Thus this risk model assumes a linear dependence of risk on dose, with the numeric value of the slope being dependent both on sex and time since exposure.

In addition to the problem of extrapolating from high to low doses implicit in the model described above, there are two limitations in using the data from the atomic bomb survivors study for fitting this model. The first is that doses in this study were received in a single exposure and at a very high dose rate. The second is that the exposed cohort consisted of Japanese subjects, and thus extrapolating results to a North American population with rather different population lung cancer rates, especially for females[4], involves the "transport" problem, i.e. the problem of the appropriate risk model to use in North American populations. For these reasons, the existence of a large body of data from the Canadian study of cancer following multiple fluoroscopies is of considerable utility in supplementing the data from the atomic bomb survivors study. The Canadian study (described in more detail below) involves highly fractionated exposures at much lower dose rates than the atomic bomb survivors study, and of course the population involved was North American.

The present report describes in detail the estimation of lung tissue doses for individual subjects in the Canadian study, and gives results with respect to lung cancer mortality observed in the cohort between 1950 and 1987. Detailed consideration is also given as to sources of error in the dose estimation procedures, but no attempt has been made to numerically correct for the potential effects of such measurement error in the present report.

2. The Canadian Study of Cancer Following Multiple Fluoroscopies

The cohort consists of 92,707 subjects first treated in a Canadian institution for tuberculosis (TB) during the period 1930-1952. During the 1930's and 1940's, and prior to the introduction of antibiotics to treat TB in the early 1950's, a common form of treatment was to partially collapse the lung, a process known as artificial pneumothorax. The assumption was that if part of the lung was at rest, there was less likelihood of bacterial spread in the lung tissue. The process of artificial pneumothorax involved admitting air to the chest cavity, and in order to monitor this process, chest fluoroscopy was widely used. Such fluoroscopy involved the exposure of several organs of interest to external low-LET radiation. Since pneumothorax was typically carried out at intervals ranging from daily to

biweekly, and often over several years, patients receiving pneumothorax were exposed to repeated low levels of low-LET radiation. Organs of particular interest in this context include the female breast, the lung and the thyroid.

A study was initiated in 1973 by the Epidemiology Unit of the National Cancer Institute of Canada. Teams of extraction clerks visited all institutions in Canada which had treated TB patients some time between 1930 and 1952, and which still had available the relevant records at the time of data collection (1973-1976). Data were obtained from all provinces except Newfoundland, where all records had been destroyed prior to the start of the study.

All individual patient files were searched by the clerks, and information extracted onto a standard data collection form. The data collected consisted of identifying information such as given name, surname, and date of birth, details of TB diagnosis, details of treatment for TB, and follow-up information such as date of last contact. The treatment information extracted related primarily to treatment by artificial pneumothorax. For each series of pneumothorax received by a patient, information was recorded on the starting and ending date of the series, the number of treatments received, and/or the rate of such treatments. Details were also collected on related treatments such as fluoroscopy without pneumothorax, and aspirations. In addition, data were also extracted relating to treatment by lobectomy, thoracoplasty, pneumolysis, and antibiotics.

The completed data extraction forms were sent to the NCIC Epidemiology Unit for coding, and data entry and processing. A total of 110,088 usable records was received. Since one individual could have been admitted to more than one institution, it was first necessary to identify records which referred to the same individual. For this process a computerized internal record linkage was conducted. In this process, elements of identifying information such as given names, surnames, and dates of birth are used to identify such records. Conceptually each record is compared with every other record, and a probabilistic weight is computed which is a measure of the relative odds in favour of any two records being a match (i.e. referring to the same individual). In practice it is necessary to restrict the actual

comparisons made in order to make the exercise logistically feasible. Thus, comparisons are usually restricted to records which have a common value for some identifier which is thought to be recorded with a high degree of accuracy. In the present context, a code derived from the surname (the NYSIIS code) was used. The general purpose computer system used to carry out such record linkages and the method for computing probabilistic weights have been described in detail.[5]

Following completion of the internal record linkage, records referring to the same individual were brought together in order to form a composite treatment history. This resulted in the formation of a cohort of 92,707 individuals, which constitutes the cohort for follow-up.

Mortality in the cohort between 1950 and 1987 has been determined using the same process of computerized record linkage to link the records from the cohort to the Canadian National Mortality Data Base. The latter data base contains machine readable records of all deaths occurring in Canada since 1940, together with those of Canadian residents dying in the US. The data base contains identifying information, and fact and date of death, and since 1950, the underlying cause of death coded to the appropriate revision of the International Classification of Diseases.

Several linkages of the fluoroscopy cohort to the mortality data base have been completed. The first such linkage was to mortality records between 1950 and 1977, and this was subsequently supplemented by linkage to the 1978-1980 death records. A third linkage was to the mortality data between 1940 and 1949. Thus, mortality between 1940 and 1980 available from these three linkages has been used to examine breast cancer mortality in the 31,710 women known to be alive at the start of 1950, as described below.

A fourth record linkage between the cohort records and the Canadian National Mortality Data Base to the end of 1987 has recently been completed. This linkage involved relinking all records to mortality since 1940, using an improved updated linkage system. Thus, the links currently available for analysis may differ to a minor degree from those utilized in the

breast cancer analysis, due to improvements in the methodology.

An extensive statistical analysis of the breast cancer mortality results between 1950 and 1980 has been reported.[6] A total of 163 deaths from breast cancer was observed in those women who received breast tissue doses of 0.1 Gy or greater, compared to an expected number of 102 based on age and calendar year specific Canadian national breast cancer mortality rates. In contrast, amongst those women with breast tissue dose less than 0.1 Gy, there were a total of 319 observed deaths from breast cancer, compared to an expected of 281. The relative risk of breast cancer mortality comparing the "exposed" cohort (i.e. those with breast tissue doses $\geq$ 0.1 Gy) was 1.36 (95% confidence interval 1.11 - 1.67) relative to the "unexposed" cohort. There was an increase in risk of death from breast cancer with increasing dose, with women in the highest dose group ($\geq$ 10 Gy) having a rate approximately 36 times that of those with less than 0.1 Gy. The data were best fitted by a simple linear dose-response model with the slope of the line being modified by age at first exposure, time since first exposure, and whether the patient had been treated in the province of Nova Scotia or elsewhere in Canada. The latter distinction is of particular importance with respect to breast tissue dose, since fluoroscopies in Nova Scotia were primarily given in the anterior/posterior (AP) orientation, whereas in the rest of the country they were almost exclusively given in the PA orientation. Thus, in Nova Scotia, doses to breast tissue were much greater than those in the rest of the country. The slope of the line, i.e. change in risk per unit of dose was substantially greater in Nova Scotia compared to the rest of the country, and this anomaly remains to be resolved.

There was a marked influence on the slope of the dose-response relationship of age at first exposure. Women first exposed between ages 10 and 14 were at greatest risk, and those first exposed past the age of 35 had very little increase in risk. No increase in mortality was seen until women had attained the age at which the background rate of breast cancer mortality increases (from about age 30 on), and until at least five years had elapsed since first exposure. There was some evidence of a peaking in the dose-response relationship some 25-34 years after first exposure, after which risks somewhat decreased. Inclusion of

age at first exposure, and time since first exposure terms in the risk model led to rather similar projections of lifetime risk estimates under both the additive and relative risk models. It was concluded that if the risk model was valid, any risk from the induction of breast cancer by repeated exposures to mammographic screening would be outweighed by even a very minimal benefit to be derived by such screening.

To date, only the breast cancer mortality experience among the women in the cohort has been analyzed. The present report covers the estimation of lung tissue doses for all subjects (both female and male) enroled in the cohort, the examination of sources of error in these estimates, and a preliminary analysis of the lung cancer mortality results between 1950 and 1987.

B. THE DOSE MODEL

1. The Components of the Dose Model

The objective in deriving an appropriate dose model is to be able to estimate as accurately as possible for each individual subject in the cohort the dose accumulated by lung tissue as a consequence of repeated fluoroscopy exposure. Essentially therefore, the model has two components, namely obtaining a count of the number and type of fluoroscopies received by each individual subject as a function of time and place, and the dose to lung tissue resulting from each particular fluoroscopic exposure. Conceptually it is possible to obtain an individual subject count with respect to number and type of fluoroscopies, since the relevant information was detailed in each individual patient's medical record. However, it is not possible to estimate at the individual level the organ dose consequent upon a particular fluoroscopic experience, since of course there was substantial variation in the values of those parameters which determined dose such, for example, as exposure time. Therefore, in practice, the required dose model inevitably involves some degree of averaging of those parameters which determine patient entrance exposure and hence organ dose.

It is possible to subdivide the component of the dose model which involves estimating organ dose into three further components. These are the radiation output produced by

fluoroscopes of the type and vintage utilized during the relevant time period (primarily the 1930's and 1940's when artificial pneumothorax was widely used), the estimation of the organ dose received as a function of the output of the fluoroscopes, and the estimation of the values of those physical parameters such as time and tube kilovoltage which determine both the output of the fluoroscope and the organ dose received. Therefore, it is possible to identify four separate components of the dose model, namely the three which determine organ dose and the estimation of individual fluoroscopy counts. Each of these components is addressed in detail in the next four sections, followed by a description of the integration of these components into the dose model. The application of the dose model to the cohort data is described in Section 7. Potential errors in the dose model are discussed in Chapter C, and results with respect to lung cancer mortality are presented in Chapter D.

2. Estimating the output from fluoroscopes

The model used the radiation output exposure rate of fluoroscopes as published by Boice et al.[7] who performed direct measurements on original fluoroscopes as used at the time of the examinations. To be compatible with current SI usage, output exposure rate has been converted to air kerma rate in grays/minute at the surface of the patient (33cm from the focal spot). These data have been used to derive a function to predict the output K in Gy/min as:

$$K = (c_1 \times kV - c_2) \times mA$$

where kV is the applied kilovoltage, mA is the tube current in milliamperes and c_1 and c_2 have values of 2.01×10^{-3} and 6.17×10^{-2} respectively prior to the addition of filtration (HVL = .85mm Al) and 1.10×10^{-3} and 4.11×10^{-2} after the additional aluminum filtration (HVL = 1.6 mm Al).

3. Estimating organ dose as a function of surface air kerma

The values of lung dose in grays per entrance air kerma (also in grays) were calculated for each condition of patient orientation and beam collimation. The estimated dose, D, to the

lung for a specific examination is given by:

$$D = K \times \frac{t}{60} \times f \times \sum_i p_i \times d_i$$

where K is the air kerma output rate of the fluoroscopy unit at the entrance surface of the patient (grays/min), t is the exposure time in seconds per examination, and f is the number of examinations per treatment. The product of these factors gives the total air kerma received at the surface of a patient, per treatment. It is then multiplied by the summation over all conditions i under which irradiation was carried out of d_i (Table 1), the estimated dose to the lung in grays per air kerma at the patient entrance surface for condition i weighted by the fraction, p_i, of total examination time to which condition i applies (Table 3). The exposure conditions which influence the value of d_i depend on patient orientation (PA or AP), shuttering (collimation) of the x-ray beam and half-value layer (HVL) of the beam. Values of d_i were obtained using the programme "CDI3"[8] provided by the Center for Devices and Radiological Health, FDA in Rockville Md. The algorithm uses the results from the Monte Carlo data of Rosenstein et al.[9,10] for exposures to a standard reference man and woman. For the unshuttered exposures a field size of 40.6 cm x 27.9 cm centred at 7.6 cm above the xiphoid process was used while for the shuttered configuration the field size was 20.3 cm x 27.9 cm centred vertically at the same position, but shifted 10 cm from the midline.

Table 1: Factors Used to Convert Air Kerma Incident on Patient to Absorbed Dose to the Lung d_i (Gy dose / Gy air kerma)

View	Sex	Shuttering	No Filter d_i	Filtered d_i
PA	M	N	.068	.157
PA	F	N	.071	.165
AP	M	N	.079	.182
AP	F	N	.060	.136
PA	M	Y	.034	.079
PA	F	Y	.036	.084
AP	M	Y	.039	.091
AP	F	Y	.030	.068

4. Estimating exposure parameters

Parameters such as time, tube current, and kilovoltage used for fluoroscopic exposure were determined through interviews with physicians who had used artificial pneumothorax in Canada since the 1930's. Approximately 210 physicians with relevant fluoroscopic experience were located, 91 of whom completed a detailed questionnaire given by a trained interviewer. The completed questionnaires represent an aggregate of 644 man-years of experience in 43 different treatment institutions across the country (Table 2). Although no interviews were conducted in Newfoundland or Prince Edward Island, only about one percent of the total patient records comes from these two provinces.

Table 2: Coverage of the Physician Interview Series, by Province

Province	Number Interviewed	Number of Institutions Represented	Total No. Man-years of experience
Nova Scotia	23	9[a]	128
New Brunswick	2	2	2
Quebec	7	6	44
Ontario	23	13	163
Manitoba	5	3	92
Saskatchewan	10	2	50
Alberta	11	4	90
British Columbia	9	4	75
Totals	91	43	644

[a] Includes private practice and travelling chest clinics

The first purpose of the questionnaire was to fix a physician's experience in time (start of practice and duration) and space (province and institution). Secondly, information was elicited regarding the actual fluoroscopes used (manufacturers), the machine set-up (the presence or absence of filtration, current and kilovoltage settings), field sizes, and any changes in the controls which may have been made during a screening. The third major part of the questionnaire related to the typical management of a patient in a single screening session (number of exposures per session, initial patient orientation, duration of exposure, frequency and extent of patient rotation) and throughout a course of lung collapse treatment (total number of screens, frequency of screening, number of screens after collapse discontinued, in- and out-patient differences).

Although fluoroscopy may have been available for a wide range of procedures, it was apparently seldom used except in conjunction with artificial pneumothorax and artificial pneumoperitoneum. Very little information was supplied regarding the use of fluoroscopy as an adjunct to oleothorax, chest aspiration, lobectomy, pneumonectomy, gastro-intestinal series, pneumolysis, thoracotomy, phrenic crush and routine chest exams (instead of x-ray films).

It was also apparent that fluoroscopic screening was practised in a highly individualistic manner with some differences in technique even between physicians practising in the same institution at the same time. The screening routine varied from patient to patient depending in part on the stage of disease, stage of treatment, other concurrent therapeutic measures, and even the degree of patient obesity.

Questionnaire responses were coded, weighted by the estimated total number of screenings carried out by the individual, and averaged by province for values required in the dose model. An attempt was made to find time trends and institutional differences in various responses but none could be determined with the available data.

Considerable spatial variation is evident at the provincial level although many of the extreme values are based on a relatively small number of responses and are not considered to represent unique regional practices. However, the difference in the proportion of screens with an initial AP patient orientation between Nova Scotia, where this was common, and the other provinces, where it was not, is well recognized and is strongly confirmed in these responses. Since initial orientation to the x-ray source has important absorbed dose implications for organ sites near the surface of the body (particularly the female breasts and the spinal red bone marrow), the current dose model distinguishes Nova Scotia from the rest of the provinces. Although patient rotation was occasionally employed during fluoroscopy, the degree of rotation was small, would have little effect on lung tissue dose, and was therefore not considered in the dose model. The responses also indicated that filters came into general use about 1945 and usually comprised 1.0 mm of aluminum. Since the addition

of such a filter substantially lowers the radiation output and increases the penetrating power of the beam, the current dose model distinguishes pre-1945 (unfiltered) exposures from subsequent (filtered) ones. Table 3 summarizes the parameters obtained from the physician interviews which were incorporated in the dose model.

Table 3: Parameters Obtained from Physician Interviews Used in Dose Model

Parameter	Nova Scotia	Other Provinces
Exposure time (seconds)	12.5	10.0
Milliamperage	4.8	4.3
Kilovoltage	71	75
AP Orientation (%)	90	0
PA Orientation (%)	10	100
Shuttering used (%)	19	19
Shuttering not used (%)	81	81
Filtration added (year)	1945	1945

5. Estimating fluoroscopy histories for individual study subjects

The raw data for estimating counts with respect to number and types of treatments related to artificial pneumothorax consisted for each treatment series of the following: the type of treatment (see Table 4); the day, month, and year of the start of the series; the day, month, and year of the end of the series; the total number of treatments received during that period; and the rate of treatments in numbers per day. The other factor involved in this component of the dose model was the admission history for each patient. The latter contained, for each recorded admission, the institution where the admission occurred, whether or not the admission was on an outpatient basis, the day, month, and year of admission, and the day, month, and year of discharge.

Table 4: Types of Treatment Involving Fluoroscopy

1.	Pneumothorax (right)
2.	Pneumothorax (left)
3.	Pneumothorax (side unknown)
4.	Aspiration (right)
5.	Aspiration (left)
6.	Aspiration (side unknown)
7.	Fluoroscopy without refill (right)
8.	Fluoroscopy without refill (left)
9.	Fluoroscopy without refill (side unknown)
10.	Pneumoperitoneum

Following completion of the internal record linkage, each patient potentially had available a number of treatment series, and a number of admission series. Inevitably some data were missing for some study subjects, and therefore a certain degree of interpolation and extrapolation was necessary, as described subsequently. As described above, it was concluded that the primary determinants of patient entrance exposure were time and place. The time element was subdivided into two categories, namely up to and including 1944, and 1945 or later, corresponding to the addition of aluminum filtration to fluoroscopes generally at that time. The other important aspect of the time component was to allow for the proper computation of person-years at risk and estimation of the time dependency of any radiation effect required by the statistical analysis. For the latter purpose, it is adequate to express time units in terms of individual years. Place was dichotomized into two categories, namely whether the exposure had been received in a Nova Scotia institution or not, and thus whether or not the orientation was treated as 90 percent AP or 100 percent PA, respectively.

Therefore, the required output from this phase of the dose model was for each individual

subject a count of the number of treatments classified by treatment type, single calendar year, and whether or not treatment occurred in Nova Scotia.

The first step in estimating fluoroscopy counts for each study subject was to compute a comprehensive admissions history. As indicated above, this involved both interpolation and extrapolation for missing data, and also resolving any possible overlap in time of admission. The latter could occur by mistake, or by duplicate recording of the same admission in records emanating from different institutions. The procedure employed to compute the comprehensive admission history was as follows.

The objective in deriving the comprehensive admission history was to determine for each half month between 1930 and 1969 inclusive the province (Nova Scotia or non-Nova Scotia) in which the subject was most likely to be admitted. Half months were used as it was considered that this time period was sufficiently accurate for the required purpose. It also allowed for a discharge and subsequent admission to occur in the same month, a not uncommon occurrence for TB patients transferred from one institution to another. The procedure employed was to set up for each subject an admissions matrix of dimension 2 by 3 by 960. The first element referred to whether or not the admission took place in Nova Scotia, the second element had three possible values of "certainty" code, corresponding to definite, probable, and possible admissions, and the third element referred to the half months starting with the first half of January 1930, and ending with the last half of December 1969. It was assumed that any record referring to fluoroscopy received after 1969 was in error, since the practice of artificial pneumothorax was generally discontinued in the 1950's, though a few were conducted in the 1960's.

In order to complete the matrix for each study subject, each admission series for that subject was considered in turn. It was first determined whether the institution code corresponded to Nova Scotia or a non-Nova Scotia province. The half month of admission and the half month of discharge were then computed. If information on both month and year of admission and discharge was available, then the second matrix element was incremented by

a count of 1, with a certainty code of "definite". If month and year of admission, and year of discharge were known, but the month of discharge was missing, then all half months starting from admission to the end of the year prior to discharge were incremented with a certainty code of "definite". All half months in the year in which discharge took place were then incremented with a certainty code of "probable". The analogous procedure was used when the only missing date information was month of admission. When year of admission and discharge were both known, but month of admission and discharge were not available, half months during the year of admission and the year of discharge were treated as "probable", with any intervening years being treated as "definite". For records in which either year of admission or year of discharge was missing, the matrix was incremented with a certainty code of "possible" either from the start of 1930 or to the end of 1969 as appropriate for all those years except that which contained a known year of either admission or discharge, the latter year being set to "probable". Thus, in summary, if the subject was known to be admitted during a specific month, the corresponding code was "definite", if the subject was known to be admitted some time during a year, but the month was unknown, all months for that year were set to "probable", and if the patient had been admitted or discharged but with no corresponding discharge or admission date, the remainder of the entire period (1930-1969) was set to "possible". It must be emphasized that the object of the exercise was not to determine whether or not a patient was admitted in any particular month, but rather, if they received a fluoroscopy during that month, the province in which it was most likely to have been received. It should also be noted that the identical dating procedure was used for treatment records as described below, and thus treatment records are logically assigned to the correct half month as determined by the admission history.

Following completion for each study subject of the matrix containing the count of admission histories classified by province, certainty code and half month, the most likely province of admission for each half month between 1930 and 1969 was then computed. The decision rules for this process were as follows. For each half month, if any "definite" data were available, the proportion of admissions in Nova Scotia was calculated as the ratio of the counts of "definite" records emanating from Nova Scotia, to the total number of "definite"

records for that subject. Similarly, if only "probable" data were available the same computation was carried out using the "probable" data, and if only "possible" data were available then the procedure was repeated using the "possible" admission records. Finally, a weighted average proportion of Nova Scotia admissions was computed for each individual subject in which definite values, probable values, and possible values were weighted (arbitrarily) with values of 3, 2, and 1 respectively. This procedure was then used to compute a weighted proportion, and this value was applied to all half months for which no direct data were available.

In summary, following this procedure it was possible for any half month between 1930 and 1969 to determine the likely proportion of admissions (and therefore treatments) which took place in Nova Scotia as compared to the other provinces. This factor could then be used to weight the dose arising from that particular treatment using the appropriate combination of parameters corresponding to Nova Scotia and the other provinces.

The second step in computing the count of fluoroscopies, was to determine the treatment history for each individual study subject. This was carried out as follows.

A composite treatment history for each study subject was computed. Each treatment series for that subject was classified by treatment type (see Table 5), and, as for the admissions history calculation, a starting and ending half month were computed for the particular series. If both month and year of starting the series were unknown, a default value was supplied based on the average value for complete records for all subjects. (Default values used in the treatment calculation procedure are shown in Table 5). For series of unknown duration a default duration value was supplied, which was a function of both treatment type, and whether or not the treatment series had been completed within one year. It appeared from inspection of complete records, that there were two distinct patterns, i.e. those where the series took place within a year, and those which took place over a longer period. A "certainty" code was attached to each treatment series as for the admissions history calculation depending on the availability of month and year of starting and ending the series.

The treatment rate was computed as the ratio of the number of treatments in that series to the duration of that series, if the number of treatments was available. If not, the rate of treatment as recorded in institution records was used. If the latter value was not available a treatment specific default rate value was used (Table 5).

Table 5: Default Values for Treatment Calculations

Treatment	Default Duration (Months)[a]	Default Duration (Months)[b]	Default Starting (Month and Year)	Default Rate Per Month
Pneumothorax (right)	7	3	July 1942	3.372
Pneumothorax (left)	7	3	July 1942	3.372
Pneumothorax (side unknown)	7	3	July 1942	3.372
Aspiration (right)	2	1	July 1943	2.000
Aspiration (left)	2	1	July 1943	2.000
Aspiration (side unknown)	2	1	July 1943	2.000
Fluoroscopy without refill (right)	4	2	July 1943	1.666
Fluoroscopy without refill (left)	4	2	July 1943	1.666
Fluoroscopy without refill (side unknown)	4	2	July 1943	1.666
Pneumoperitoneum	7	4	July 1950	4.000

[a] Series starting and ending in different calendar years
[b] Series starting and ending in the same calendar year

Following completion of the matrix of treatment records for each individual subject, overlaps and conflicts were resolved as follows. It was assumed that any overlap in time between treatment series for the same treatment represented a duplication of recording. Therefore, for each specific treatment (Table 4), a half month by half month inspection of the data for that subject was conducted. If more than one definite treatment count was available for that half month, the average number of treatments was used. If no definite data were available, probable data were used, and again, if no probable data were available, possible data were

used. Thus, at the end of this procedure, for each half month between 1930 and 1969, each subject had a specific count of the number of treatments by treatment type.

6. Integration of the components of the dose model

Following completion of the estimation of lung tissue dose per treatment as a function of two time periods (up to and including 1944, and 1945 or later) and province (Nova Scotia or other provinces) (Sections 2 - 4), it was necessary to apply these estimates to the counts derived for each study subject as in Section 5. This was done as follows.

The total dose to lung tissue received during each half month was estimated by multiplying the count of the number of pneumothorax treatments, and fluoroscopy received without refill by the appropriate factor to convert from incident air kerma to mean absorbed dose to the lung. The latter value depends both on whether the half month in question was before or after 1945, and the proportion of admissions in Nova Scotia institutions for that particular half month. The half month doses were summed for each calendar year, giving an estimated lung tissue dose for each subject for each calendar year between 1930 and 1969. The latter data constitute the dose data required for the statistical analysis described in Chapter D.

7. Implementation of the dose model

The dose model described above was applied to the data from the Canadian fluoroscopy cohort study. The original input data contained records relating to a total of 92,707 individuals, 44,758 females, and 47,949 males. The dose model was applied to all individuals, to yield the required estimates of lung tissue dose for each calendar year between 1930 and 1969.

Subsequently, a number of validity and consistency checks were carried out on the data, and Tables 6 and 7 show the criteria applied, and the number of records for females and males respectively which were eliminated by these various criteria. It should be noted that these exclusions do not necessarily represent errors in the data, but could represent outliers, i.e.

subjects with extreme but valid values. Nevertheless, to be on the safe side, such individuals were excluded from analysis. The major reason for exclusion was loss to follow-up before 1940, when the mortality ascertainment started. It should be noted that such loss to follow-up will not introduce any bias into the results unless such loss is independently associated both with exposure and disease risk, and this seems most unlikely.

Table 6: Number of Study Subjects Included and Excluded in Statistical Analysis (Females)

		No.	%
Excluded	Lost to follow-up before 1940	6,428	14
	Died 1940-1949	4,501	11
	Errors in data records	1,423	3
Included in analysis		32,185	72
Total		44,758	100

Table 7: Number of Study Subjects Included and Excluded in Statistical Analysis (Males)

		No.	%
Excluded	Lost to follow-up before 1940	7,010	15
	Died 1940-1949	6,662	14
	Errors in data records	1,773	4
Included in analysis		32,504	68
Total		47,949	100

The final data files for statistical analysis contained 32,185 females and 32,504 males, in total 64,689 subjects. Characteristics of this final cohort with respect to estimated lung tissue doses are shown in detail in Table 8, and a statistical analysis of these data with respect to lung cancer mortality between 1950 and 1987 is presented in Chapter D.

Table 8: Persons and Person-Years at Risk by Dose

Dose Category (centigray)	Females			Males		
	Persons	Person-Years	Mean Dose (cGy)	Persons	Person-years	Mean Dose (Cgy)
0	19,209	620,158	0.0	20,912	576,435	0.0
1-9	2,238	72,680	3.3	2,281	65,488	3.2
10-19	1,459	48,145	16.3	1,024	30,002	14.8
20-29	854	28,032	24.3	1,151	33,316	24.3
30-49	1,739	59,108	39.4	1,539	46,162	39.3
50-69	1,571	53,759	59.4	1,276	39,037	59.1
70-89	1,307	44,252	78.8	1,088	33,873	79.3
90-119	1,497	50,763	102.9	1,200	36,796	103.5
120-169	1,299	42,803	141.1	1,163	34,858	140.6
$\geq$ 170	1,255	40,443	256.8	1,239	35,505	268.2
Total	32,428	1,060,143		32,873	931,472	

C. SOURCES OF ERROR IN THE DOSE MODEL

1. Types of error

Two types of error may be distinguished when considering the results of any experimental or observational study. The term "random error" is applied to those sources of error which do not bias the point estimate of interest. In the present context, where the objective is to

fit a dose-response model to the observed number of deaths from lung cancer, Poisson regression models are used to fit the data as discussed in more detail in Chapter D. In this model, observed number of deaths and person years at risk are cross-classified into cells defined by appropriate combinations of variables such as dose, age at exposure and time since exposure. If the assumption is made that the hazard rate is constant within each of these cells, the observed number of deaths would follow a Poisson distribution. Random error in the results is then addressed by considering the sampling distribution of the number of deaths, and setting the confidence intervals based on the appropriate statistical distribution, i.e. the Poisson distribution. In this context random error arises because of random variations in the number of deaths which will occur in the sample selected (i.e. the cohort), and these will be distributed around the expected number of deaths (i.e. that which would be observed in a cohort of infinite size). Random error under this model is appropriately addressed by the estimated confidence intervals around the parameters included in the particular dose model being considered.

The second type of error, namely systematic error, applies to any characteristic of the study design, execution, or analysis which introduces a bias in the parameters which are being estimated. In the present context, errors in estimating lung tissue doses for individuals included in the cohort will give rise to systematic error. Even if the errors in dose assessment are regarded as random (i.e. applying equally to all members of the cohort) the resulting measurement error will still introduce a bias, which under the relative risk model used for analysis will bias the estimate towards the null. This type of error which should be referred to as non-differential rather than random error is a common phenomenon in epidemiologic studies. Statistical techniques are being developed which attempt to compensate for the resulting bias, but to date the models available are relatively simple, and cannot be directly applied to the type of complex dose-response function which is being considered for the present analysis. However, it is important to quantify as far as possible the sources of error in the dose model in order to identify the most important sources, and qualitatively assess the impact on risk estimates.

This chapter addresses each of the four components in the dose model described in detail in Chapter B. For each component, the potential sources of error are identified, and to the extent made possible by the data, the magnitude of error which might be introduced by these sources is discussed. However, as discussed above, it is beyond the scope of the present report to attempt to integrate these various sources of error into a comprehensive error model.

2. Errors in estimating the output from fluoroscopes

Radiation output would vary according to the calibration of equipment and variations in adjustment of tube current so that the output could easily be uncertain by $\pm$ 50 percent.

3. Errors in estimating organ dose as a function of surface air kerma

The calculations of dose per entrance exposure depend on rather simplistic models of the anatomy so that estimated uncertainty might be $\pm$ 60 percent.

4. Errors in estimating exposure parameters

An important contributor to uncertainty in dose estimation is the uncertainty in the values of the parameters obtained from the interviews with the 91 physicians who conducted pneumothorax during the relevant time period. Uncertainties in the following parameters will have affected the dose estimation: kilovoltage, tube current, exposure time, orientation (PA or AP) and shuttering. It should be noted that, as discussed earlier, the degree of rotation employed during examinations was usually small, and would have had little impact on lung tissue dose. It should also be noted that there was very close agreement among the physicians, and from other sources of information that filtration was added to the beam almost uniformly in 1945, so any error in assuming presence or absence of filtration is likely to be negligible.

The parameter used for tube kilovoltage affects the radiation output of the fluoroscope through the linear function described by Boice et al.[11] The mean kilovoltages estimated from the physician interviews were 71 and 75 kv for Nova Scotia and the other provinces

respectively. Since these values are so similar, the combined standard deviation was estimated as ± 17.8 Kv. When the output of fluoroscopes is estimated using kilovoltages one standard deviation away from the mean, the corresponding percentage changes in output are 44, 54, 40, and 48 percent for Nova Scotia before and after 1945, and for non-Nova Scotia before and after 1945, respectively. The kilovoltage data are approximately normally distributed, so these percentages represent an approximate error range which would include about 2/3 of the corresponding values for the output.

The outputs from the fluoroscopes are directly proportional to exposure time and tube current. Again, the mean values for these two parameters for Nova Scotia and the other provinces are similar, having values respectively of 12.5 and 10 seconds, and 4.8 and 4.3 milliamperes, respectively. Therefore, data for physicians from Nova Scotia and the other provinces were again combined. The distribution of exposure times is very skewed, and is not fitted well by either a normal or log normal distribution. Therefore, distribution independent methods were used to examine the data. The median of the distribution of exposure times is 10 seconds, with a lower 15 percentile of 5 seconds, and an upper 85 percentile of 37.5 seconds. Therefore, approximately 70 percent of exposure time values might be expected to lie between 0.5 and 3.75 x the value used in the dose estimation procedure. These factors would, of course, apply directly to the corresponding change in the output of the fluoroscopes.

The distributions of estimates of tube current were fairly closely distributed around their mean values. The standard deviation for the combined data for Nova Scotia and the other provinces is 1.4 milliamperes. Thus, given a normal distribution, approximately 70 percent of tube current values would lie between 4.6 ± 1.4, corresponding to a percentage change in output of ± 30 percent.

The two other parameters estimated from the interview with the physicians and used in the dose model were the orientation (PA or AP) and whether or not shuttering was employed during fluoroscopic examination. With respect to orientation, 18 of the 23 physicians from

Nova Scotia reported that they never used the PA orientation, and the remaining 5 indicated that, at most, they used it during 10 percent of examinations. Thus, it appears that a negligible amount of exposure in Nova Scotia was incurred in the PA orientation. In terms of the current dose model, orientation impacts upon the value of the parameter converting incident air kerma to absorbed dose. Since these only differ by about 15 percent for AP and PA orientation, it would appear that in the province of Nova Scotia any deviation from the assumed 90 percent AP orientation would constitute a negligible error in estimating lung tissue dose compared to that which may result from the uncertainty in the exposure time. In provinces other than Nova Scotia the amount of PA orientation employed was more variable than in Nova Scotia, but only 20 percent of the physicians interviewed employed more than 10 percent AP orientation during examinations. Therefore, it would appear that the assumption made in the dose model is reasonable, and any departure from the parameter estimate used in that model (i.e. 100 percent PA orientation), would again lead to a negligible error in view of the essentially small differences between the dose per kerma values for lung tissue from PA and AP orientation.

With respect to whether or not shuttering was employed, the weighted average proportion of physicians who employed shuttering regularly was 81 percent. Approximate confidence intervals may be set around this estimate using the binomial distribution. This suggests that about 70 percent of values should lie approximately between 76 percent and 86 percent. Presence or absence of shuttering has an impact on the dose per kerma value for lung tissue. However, for grouped data, the assumption that 81 percent of exposures involved shuttering should not lead to any substantial error.

5. Errors in estimating fluoroscopy histories for individual study subjects

The fourth component to the dose model was the estimated count of fluoroscopies for each patient as a function of time (calendar year) and place (Nova Scotia or other provinces). Inevitably errors will have occurred in this process due to data which were missing in the original sanatorium records, or which were misrecorded. There is no way of assessing the magnitude of this problem. Anecdotally, all records appear to have been kept except for

the province of Newfoundland where all records were destroyed. This latter problem will only affect individuals treated both in Newfoundland and other provinces, and the extent of this practice is unknown. Again anecdotally, accurate records appear to have been kept of all pneumothorax treatment, so misrecorded or missing data within a particular institution does not appear likely to constitute a major error.

The primary source of error which can be assessed in the process of counting pneumothorax treatments lies in the necessity for extrapolation and interpolation discussed in Section B.5. Tables 9 and 10 show the distribution of treatment series classified by the amount of missing information separately for females and males. Treatment series with missing month of start or end of series are unlikely to be seriously in error. For the females, 15.8 percent of study subjects had at least one treatment series in which the year of either start or end of the series was unknown. The corresponding proportion for males is 13.0 percent. As discussed previously, default values were used where data were missing. This would be particularly important for the 15.8 percent of females and the 13.0 percent of males for whom year information was missing, but in view of this relatively small percentage and the reasonable consistency of treatment practices across institutions this seems most unlikely to have introduced any serious error. Tables 9 and 10 show the number of records which had neither the number of treatments nor the rate of treatment available. Where either one of these was available, presumably any error would be minimal. Again, it appears that missing information (also supplied from default values) for the number or rate of treatments is relatively unimportant.

Table 9: Distribution of Treatment Series Records by Missing Information (Females)

Start		End		Treatments: No. and Rate			
Month	Year	Month	Year	Both Missing	No. Missing	Rate Missing	Both Present
Present	Present	Present	Present	9,655	8,909	20,203	4,683
Missing	Present	Present	Present	773	135	34	5
Missing	Missing	Present	Present	4,898	9,348	3,322	230
Present	Present	Missing	Present	587	52	24	6
Missing	Present	Missing	Present	1,098	22	61	0
Missing	Missing	Missing	Present	715	61	118	0
Present	Present	Missing	Missing	1,531	166	473	15
Missing	Present	Missing	Missing	721	1	24	0
Missing	Missing	Missing	Missing	352	18	104	2

Table 10: Distribution of Treatment Series Records by Missing Information (Males)

Start		End		Treatments: No. and Rate			
Month	Year	Month	Year	Both Missing	No. Missing	Rate Missing	Both Present
Present	Present	Present	Present	8,934	6,858	19,319	3,643
Missing	Present	Present	Present	690	139	22	2
Missing	Missing	Present	Present	4,803	7,151	3,398	122
Present	Present	Missing	Present	435	49	16	4
Missing	Present	Missing	Present	731	22	54	1
Missing	Missing	Missing	Present	617	59	125	1
Present	Present	Missing	Missing	1,389	146	421	11
Missing	Present	Missing	Missing	592	6	22	0
Missing	Missing	Missing	Missing	338	20	80	1

6. Overall assessment of sources of error in the dose model

From the above discussion, it is apparent that there are a number of sources of potential error in assigning lung tissue doses to individual members of the cohort. In general, these errors appear to be non-differential, and are likely to operate to the same degree for all members of the cohort. Thus, the overall effect is likely to be a downward bias in the risk estimates, though the magnitude of such a bias cannot be quantified in the absence of the appropriate complex error model. The most important sources appear to be uncertainty as to the parameters associated with the operation of fluoroscopes, as estimated from the interview with the physicians. Of these parameters, the greatest uncertainty appears to relate to exposure time where times could easily vary from about 5 to about 38 seconds, as compared to the mean values of 12.5 and 10 seconds used respectively for Nova Scotia and the other provinces. It should be noted that the effect of this phenomenon would be to misclassify a certain proportion of individuals when dose categories are established for statistical analysis. This produces a tendency to increase the estimated risk at low doses and underestimate the risk at higher doses, and thus to dilute the strength of the dose-response relationship. This is a phenomenon which affects all epidemiologic studies in general, and studies of radiation and cancer in particular, and it is a necessary caveat to bear in mind when considering results of such studies. It is worth noting that the issue of systematic measurement error has not been addressed directly in the analysis of the atomic bomb survivors data on which current lung cancer risk estimates are based, and this problem has to be borne in mind when considering the results of the present study compared to that of the atomic bomb survivors.

D. LUNG CANCER MORTALITY (1950-1987) FOLLOWING REPEATED CHEST FLUOROSCOPIES IN A COHORT OF 64,689 CANADIAN TUBERCULOSIS PATIENTS

1. Introduction

This chapter contains results from the analysis of the lung tissue dose data estimated as described in Chapter B and applied to lung cancer mortality observed in the cohort by computerized record linkage. The focus is on the shape and magnitude of the dose-response

relationship, and of the modifying effects of sex, age at first exposure, and time since first exposure. In particular, results are contrasted with those presented in the BEIR V[12] Report, which applied similar statistical methods to those described here to the atomic bomb survivors data with respect to lung cancer mortality. This comparison is of particular interest, since the lung doses received in the present study were highly fractionated and generally at lower dose rates than those received by the atomic bomb survivors. This therefore provides an opportunity to assess quantitatively the effect of these latter parameters on risk estimates.

2. Methods

The assembly of the cohort has been described in Chapter A and in Reference 6. Briefly, a total of 110,088 records were extracted from Canadian institutions which had treated tuberculosis patients in the 1930's and 1940's. Subjects included were those who had first been admitted between 1930 and 1952. Internal computerized record linkage was used to identify records which refer to the same individual, and these were then amalgamated to form comprehensive records for those individuals. A total of 92,707 individuals thus constituted the cohort for follow-up.

Follow-up was conducted by linking the cohort records to Canadian mortality records between 1940 and 1987. Cause of death was not available until 1950, so those who died between 1940 and 1949 could not be included in the present analysis.

Subsequent to the mortality linkage, lung tissue doses were estimated as described in Chapter B for each individual in the cohort. A number of subjects had to be excluded from the final cohort for analysis for various reasons, as detailed in Tables 6 and 7 of Chapter B. Thus, the final cohort for analysis consisted of 64,689 individuals, 32,185 females, and 32,504 males.

For statistical analysis, observed deaths from lung cancer and person-years at risk were grouped by lung dose (0, 1-29, 30-89, 90+ Cgy), sex, age at first exposure (0-14, 15-24, 25-34,

35+), time since first exposure (10-14, 15-24, 25-34, 35+), age at risk (0-24, 25-29..... 80-84, 85+), and calendar year at risk (1950-1954, 1955-1959..... 1980-1987). An individual started contributing person years at risk either at the beginning of 1950, or else at the time of first admission, whichever was later. Person years continued to be contributed either to the end of 1987 if the subject was still alive, or to the midpoint of the year in which death occurred.

Relative risks were estimated by dose, and by sex, age at first exposure, and time since first exposure. For these estimates, the observed and person-years were stratified by age at risk and calendar year at risk, and maximum likelihood techniques were used for point estimates. P-values were based on the Mantel-Haenszel χ^2 statistic[13] and confidence intervals were based on Cornfield's approximations.[14] In addition, Poisson regression models were used to fit quantitative linear dose-response relative risk models to the data, the latter being the preferred model for lung cancer mortality used by the BEIR V Committee in their analysis of the atomic bomb survivors data. In this approach the background rate is represented by a series of stratum-specific parameters corresponding to possible combinations of age at risk and calendar year at risk. The relative risk is then modelled as:

$$RR(D) = 1.0 + \alpha_1 D \exp(\beta_1 Z_1 + B_2 Z_2 + ...)$$

where RR (D) is the relative risk for dose D, α_1 describes the linear increase in risk per unit of dose, and Z_1 Z_2 etc. are potential modifying factors such as sex or age at first exposure, with β_1 β_2 etc. being the corresponding coefficients. The computer programme AMFIT was used to fit the latter model.

3. Results

A total of 64,689 subjects (32,185 females and 32,504 males) were known to be alive at the start of 1950 and thus eligible for inclusion in the cohort for analysis. Linkage to the mortality data file between 1950 and 1987 resulted in identification of a total of 26,775 deaths in the cohort. Observed and expected values for all causes of death were computed separately for females and males, and for those with no lung tissue dose from fluoroscopy

("unexposed") and for those with some dose ("exposed"). Expected values were based on sex, age, and calendar year specific Canadian national rates for all cause mortality. The observed values (expected) for female unexposed, female exposed, male unexposed, and male exposed were respectively 6642 (6,228), 3,713 (3,095), 10,709 (11,771), and 5,711 (5,583). Detailed assessment of the pattern of causes of death is beyond the scope of the present report. However, it should be noted that the excesses seen in three of the four subcohorts is driven primarily by deaths from tuberculosis.

Tables 11 and 12 show some characteristics of the study cohort classified by sex and four categories of lung tissue dose. The latter categories were chosen to give approximately equal numbers of individuals and person years in the three categories of exposed subjects. Examination of these tables shows some patterns. Women in the high dose categories tended more often to be ever married compared to those in the lowest category, though the same pattern is not apparent for males. The mean year of birth is unrelated to dose category for females, but for males there is a trend of increasing birth year with increasing dose. The three variables relating to TB diagnosis show distinct patterns. Essentially, as would be anticipated, all those receiving lung tissue doses had diagnoses of pulmonary TB, whereas about 20 percent of those with no dose had other forms of TB. The severity of the condition was much more marked in those who received fluoroscopy and thus lung tissue doses, as indicated by the much higher percentage of bacillary positive cases, and of those with advanced stage of the disease. Although these latter factors are associated with dose, statistical analysis shows they are not confounders since they are not related to subsequent risk of lung cancer, and therefore these factors do not need to be included in the risk model.

Table 11: Characteristics of the Cohort by Dose (Females)

Characteristic	Dose Category (centigray)			
	0 (%)	1-29 (%)	30-89 (%)	90+ (%)
n	19,078	4,488	4,580	4,039
Mean dose	0.00	11.4	57.4	162.9
Ever married	12,590 (66)	3,118 (70)	3,140 (69)	3,084 (76)
Never married	6,488 (34)	1,370 (31)	1,440 (31)	955 (24)
Mean birth year	1917	1916	1918	1918
Pulmonary TB diagnosis	15,230 (80)	4,400 (98)	4,555 (>99)	4,029 (>99)
Bacillary status positive	7,407 (39)	3,462 (77)	3,420 (75)	3,198 (79)
Advanced stage	3,031 (16)	1,593 (36)	1,314 (29)	1,518 (38)
Non-smoker	1,243 (7)	315 (7)	390 (9)	324 (8)
Smoker	1,380 (7)	412 (9)	493 (11)	466 (12)
No smoking data	16,455 (86)	3,761 (84)	3,697 (81)	3,249 (80)
Ratio smoker/non-smoker	1.11	1.30	1.26	1.44

Table 12: Characteristics of the Cohort by Dose (Males)

Characteristic	Dose Category (centigray)			
	0 (%)	1-29 (%)	30-89 (%)	90+ (%)
n	20,663	4,402	3,870	3,587
Mean dose	0.0	11.3	56.9	172.1
Ever married	12,010 (58)	2,606 (59)	2,161 (56)	12,144 (60)
Never married	8,653 (42)	1,796 (41)	1,709 (44)	1,443 (40)
Mean birth year	1911	1913	1916	1915
Pulmonary TB diagnosis	16,277 (79)	4,275 (97)	3,850 (>99)	3,570 (>99)
Bacillary status positive	9,620 (47)	3,673 (83)	3,235 (84)	3,154 (88)
Advanced stage	4,600 (22)	1,746 (40)	1,354 (35)	1,665 (46)
Non-smoker	712 (3)	183 (4)	135 (4)	188 (5)
Smoker	4,146 (20)	1,121 (26)	1,092 (28)	1,138 (32)
No smoking data	15,805 (77)	3,098 (70)	2,643 (68)	2,261 (63)
Ratio smoker/non-smoker	5.82	6.12	8.08	6.05

Tables 11 and 12 also show the available smoking data for study subjects. Information on smoking was only available in a relatively small number of sanatoria records, and data could only usefully be classified into non-smoker or smoker. The latter category could presumably include ex-smokers. Even these limited data are sufficient to show some patterns. For both females and males there is some evidence of increasing number of smokers with increasing dose. Thus, lung tissue dose and smoking appear to be positively correlated. Because smoking increases the risk of lung cancer, the confounding effect would be such as to overestimate risk estimates based on models which do not include smoking terms. It was not possible to analyze models with smoking terms in view of the lack of data for the majority of study subjects, and this limitation must be borne in mind when considering the results of the present analysis.

Table 13 shows estimated SMRs (computed using expected values from age, calendar year, and sex-specific Canadian population rates) separately for females and males for lung cancer mortality 1950-1987, classified into four categories of lung tissue dose.

Overall, both females and males show a statistically significant departure from expectation based on Canadian rates. However, females have an elevated rate and males have a decreased rate. This could be reflective of differing smoking patterns by sex in the fluoroscopy cohort. Consideration of the dose-specific SMRs for both females and males does not suggest any noticeable pattern of increasing risk with increasing dose, and the numbers of observed deaths are generally fairly substantial in all dose groups.

The apparent lack of even a moderate association with dose seen in the SMR analysis of Table 13 is confirmed by the data shown in Table 14. This table presents the results of an internal analysis, i.e. without reference to an external comparison group. Risks are computed for each dose group relative to the unexposed group. The relative risks are estimated over strata representing the possible combinations of age at risk and calendar year at risk, so the latter variables do not confound any possible association with radiation. None of the relative risks observed for either females or males show a statistically signficant departure from the null, i.e. a relative risk of 1.0, and the number of observed deaths in each dose group are again adequate to generate reasonably narrow confidence intervals.

Table 13: SMR's for Lung Cancer Mortality 1950-1987 By Dose

Dose Category (centigray)	Females				Males				Total			
	Obs.	Exp.	SMR	P-Value	Obs.	Exp.	SMR	P-Value	Obs.	Exp.	SMR	P-Value
0	168	136.6	1.23	0.00	593	651.9	0.91	0.01	761	788.5	0.97	0.17
1-29	35	35.2	0.99	0.53	99	147.6	0.67	<0.01	134	182.8	0.73	0.03
30-89	44	36.8	1.20	0.13	94	125.5	0.75	<0.01	138	162.3	0.85	0.03
90+	27	32.2	0.84	0.21	96	121.5	0.79	<0.01	123	153.8	0.80	<0.01
Total	274	240.8	1.14	0.02	882	1046.6	0.84	<0.01	1156	1287.4	0.90	<0.01

Table 14: Relative Risks and 95% Confidence Intervals for Lung Cancer Mortality 1950-1987 by Dose

Dose category (centigray)	Females		Males	
	Relative Risk	Observed	Relative Risk	Observed
0	1.00	150	1.00	473
1-29	0.84 (0.56-1.24)	33	0.88 (0.70-1.10)	98
30-89	1.01 (0.71-1.44)	44	0.93 (0.74-1.18)	93
90+	0.71 (0.46-1.09)	27	1.02 (0.81-1.29)	96

The effect of age at first exposure is examined in Table 15 for females and Table 16 for males. The relative risks comparing each of the three higher dose groups to the unexposed are presented separately for four age at first exposure groups. Again, data are stratified by age at risk and calendar year at risk. There is no evidence of any regular increase in risk with increasing dose for any of the age at first exposure groups. Those in the youngest age at first exposure group have only a limited number of lung cancer deaths, representing the fact that this group by the end of 1987 had an average age less than 60 years, and thus had not accumulated many person-years of experience at those ages at which lung cancer rates increase. For the older age at first exposure groups there are again a reasonable number of lung cancer deaths, and hence reasonably narrow confidence intervals, all of which include the null value of 1.0.

Table 15: Relative Risks and 95% Confidence Intervals for Lung Cancer Mortality 1950-1987 by Dose and Age at First Exposure for Females

Dose Category (centigray)	Age at First Exposure							
	0-14		15-24		25-34		35+	
	Relative Risk	Observed	Relative Risk	Observed	Relative Risk	Observed	Relative Risk	Observed
0	1.00	10	1.00	59	1.00	58	1.00	23
1-29	0.00 (0.00-11.05)	0	0.82 (0.43-1.55)	13	0.70 (0.37-1.33)	13	1.39 (0.54-3.42)	7
30-89	0.00 (0.00-7.27)	0	1.12 (0.68-1.86)	24	0.90 (0.51-1.60)	17	0.98 (0.23-3.46)	3
90+	0.00 (0.00-6.46)	0	0.68 (0.37-1.25)	15	0.61 (0.28-1.28)	9	1.55 (0.37-5.43)	3

Table 16: Relative Risks and 95% Confidence Intervals for Lung Cancer Mortality 1950-1987 by Dose and Age at First Exposure for Males

Dose Category (centigray)	Age at First Exposure							
	0-14		15-24		25-34		35+	
	Relative Risk	Observed	Relative Risk	Observed	Relative Risk	Observed	Relative Risk	Observed
0	1.00	5	1.00	100	1.00	136	1.00	232
1-29	0.00 (0.00-33.96)	0	1.10 (0.70-1.71)	27	0.82 (0.55-1.21)	33	0.80 (0.55-1.14)	38
30-89	0.00 (0.00-45.48)	0	0.80 (0.50-1.26)	25	1.07 (0.74-1.53)	41	0.94 (0.62-1.43)	27
90+	0.00 (0.00-48.01)	0	1.13 (0.75-1.70)	37	0.99 (0.67-1.46)	36	1.13 (0.72-1.77)	23

Tables 17 and 18 show relative risk estimates by dose category compared to the unexposed group by time since first exposure. The first 10 years of follow-up are excluded to allow an appropriate latent period. In addition, these years represent generally young ages at risk and therefore the number of lung cancer deaths is extremely small. Again, there is no observed pattern of increasing risk with increasing dose for either females or males in any of the periods of time since first exposure. For the later years of follow-up there are again reasonable numbers of deaths and hence reasonably narrow confidence intervals.

Table 17: Relative Risks and 95% Confidence Intervals for Lung Cancer Mortality 1950-1987 by Dose and Years Since First Exposure for Females

Dose Category (centigray)	Years Since First Exposure							
	10-14		15-24		25-34		35+	
	Relative Risk	Observed	Relative Risk	Observed	Relative Risk	Observed	Relative Risk	Observed
0	1.00	3	1.00	19	1.00	43	1.00	85
1-29	0.00 (0.00-15.34)	0	1.52 (0.58-3.88)	7	0.84 (0.38-1.80)	9	0.73 (0.42-1.26)	17
30-89	0.00 (0.00-16.20)	0	0.73 (0.17-2.69)	3	1.29 (0.66-2.48)	14	0.96 (0.60-1.52)	27
90+	0.00 (0.00-42.79)	0	0.00 (0.00-1.80)	0	0.47 (0.14-1.44)	4	0.86 (0.53-1.41)	23

Table 18: Relative Risks and 95% Confidence Intervals for Lung Cancer Mortality 1950-1987 by Dose and Years Since First Exposure for Males

Dose Category (centigray)	Years Since First Exposure							
	10-14		15-24		25-34		35+	
	Relative Risk	Observed	Relative Risk	Observed	Relative Risk	Observed	Relative Risk	Observed
0	1.00	25	1.00	122	1.00	180	1.00	146
1-29	0.85 (0.20-3.19)	3	0.78 (0.47-1.30)	20	0.80 (0.55-1.16)	36	1.07 (0.74-1.54)	39
30-89	0.92 (0.14-4.53)	2	0.86 (0.48-1.55)	15	0.91 (0.61-1.35)	33	1.08 (0.76-1.55)	43
90+	1.86 (0.26-10.77)	2	0.80 (0.39-1.64)	10	1.37 (0.94-2.00)	40	1.00 (0.70-1.43)	44

In order to maximize efficiency for estimating risk coefficients, the data were subdivided into ten groupings of dose. These categories were chosen so as to give approximately equal numbers of persons and person-years in each of the nine categories of dose. The distribution of persons and person-years by these ten categories is shown in Table 8. Table 19 shows the corresponding estimated standardized lung cancer mortality rates for 1950 - 1987, together with the corresponding number of observed lung cancer deaths. Rates are standardized both by age at first exposure and time since first exposure. Sampling variability is such that it is difficult to detect any particular pattern in the data shown in Table 19.

Table 19: Standarized[a] Rates Per 100,000 Person-Years (Lung Cancer Mortality 1950-1987) by Dose

Dose Category (centigray)	Females		Males	
	Rate	Obs.	Rate	Obs.
0	28.7	168	101.6	593
1-9	21.1	16	76.5	51
10-19	20.8	9	83.3	23
20-29	35.1	10	72.9	25
30-49	29.7	17	70.4	30
50-69	20.6	13	82.2	30
70-89	27.3	14	110.8	34
90-119	17.0	11	77.6	30
120-169	16.4	7	124.1	35
$\geq$ 170	17.1	9	76.2	31

[a] Standardized by age at first exposure and time since first exposure

A linear relative risk model was fitted to the data using the dose categories shown in Table 19. The background was stratified, i.e. was represented by a series of parameters representing the possible combinations of age at risk and calendar year at risk. Data for females and males were combined for this analysis since there was no evidence of

interaction between dose and sex in the Poisson regression models. The combined data set yielded an excess relative risk coefficient of 0.089 per gray (95% confidence interval -0.057 to 0.175) i.e. the relative risk per gray is 1.089. The very small size of the excess relative risk coefficient made it infeasible to model any modifying effects such as those of age at first exposure and time since first exposure. However, the univariate analyses shown in Tables 15-18 strongly suggest lack of any such interaction, i.e. there is no particular group in which even a moderate relationship between risk and dose is observed.

4. Discussion

In summary, the present analysis has failed to demonstrate even a moderate increase in the risk of lung cancer mortality associated with exposure to highly fractionated external low-LET radiation. The maximum likelihood estimate of the increase in the relative risk coefficient per gray is 0.089 (95% confidence interval -0.057 to 0.175). As discussed below, this contrasts with the results for lung cancer mortality seen in the atomic bomb survivors study, where risks are much higher. There is no evidence within the fluoroscopy cohort of any particular subgroup as defined by sex, age at first exposure, or years since first exposure showing any marked dependency of risk on dose.

The total number of lung cancer deaths observed in the fluoroscopy cohort (1,156) is sufficient that most of the statistical analyses conducted have good power to detect even moderate relationships between dose and risk. This is reflected in the reasonably narrow confidence intervals around a number of the relative risk estimates shown in Tables 14-18. The potential bias of most concern in the present study is of course smoking. However, the limited data available for the cohort (Tables 11 and 12) suggest that if anything, smoking and dose are positively correlated, and therefore the inability to adjust for cigarette smoking in the cohort analysis would, if anything, lead to an overestimate of the radiation related risk.

The present results contrast with the results of the BEIR V analysis of the lung cancer mortality data for the atomic bomb survivors. The relative risk for one gray derived from

the BEIR V model is 1.64 (95% confidence interval 1.07 to 2.21) for males 20 years after exposure. Because of the time dependency and sex dependency of the BEIR V model, this relative risk varies both with sex and time since exposure. Because of the very small effect seen in the present data, it is not possible to exclude the existence of sex and time dependency in the fluoroscopy data, but nevertheless it is apparent that the relative risk coefficient derived from the present analysis is substantially less than that derived from the atomic bomb survivors study. The difference between the fluoroscopy cohort analysis and the atomic bomb survivors study analysis is illustrated in Table 20. This table shows the relative risks predicted for the fluoroscopy cohort by sex, dose, and years since first exposure based on the BEIR V model. These predicted relative risks can be contrasted with the observed relative risks shown in Tables 17 and 18. It appears unlikely that the difference would have arisen by chance ($p = 0.06$).

The obvious difference between the two sets of data lies in the fact that the fluoroscopy lung tissue doses were highly fractionated and received generally at a much lower dose rate than those of the atomic bomb survivors study. This therefore suggests that there may be a substantial fractionation or dose rate effectiveness factor operating for lung cancer for external low LET exposure. This clearly would have important implications for assessing dose limits with respect to lung tissue from external low LET ionizing radiation. It is of interest to note that the relative risk estimates for breast cancer mortality based on the atomic bomb survivors and the fluoroscopy cohort are quite similar as reported in BEIR V.

Clarification of the important issues of fractionation and dose rate effectiveness should come from further follow-up, both of the fluoroscopy cohort and that of the atomic bomb survivors.

Table 20: Predicted Relative Risks in the Fluoroscopy Cohort by Sex, Dose, and Years Since First Exposure, Based on the BEIR V Model

Dose Category (centigray)	Females				Males			
	Years Since First Exposure				Years Since First Exposure			
	10-14	15-24	25-34	35+	10-14	15-24	25-34	35+
0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1-29	1.29	1.15	1.08	1.05	1.14	1.07	1.04	1.02
30-89	2.45	1.74	1.41	1.23	1.71	1.36	1.20	1.11
90+	5.25	3.16	2.21	1.67	3.09	2.06	1.59	1.33

GLOSSARY

gray (Gy):
Unit of absorbed dose of ionizing radiation i.e. energy absorbed per mass of absorber. 1 gray = 1 joule / kilogram

air kerma:
The kinetic energy transferred to electrons when a beam of ionizing radiation interacts with air at specified location per mass of that air. Unit: gray

output:
not a standard quantity. Here it is defined as the air kerma rate produced by an x-ray source, measured at a specified location (coulombs /kg-air /second) and converted to gray/minute.

Half-value layer (HVL):
the thickness of aluminum that attenuates the x-ray beam (under conditions which minimize the effects of scatter) such that the air kerma is reduced to one half of its original value.

refill:
A process of admitting air into the chest cavity in order to partially collapse the lung. This treatment was extensively used in the 1930s and 1940s for the treatment of tuberculosis. The process was also known as pneumothorax. In the present report the word "refill" refers to a particular treatment of a particular patient.

screening:
The process of examining the extent of lung collapse by using fluoroscopy. When a refill was conducted the practice was often to screen the patient before admitting air, and to re-screen after such treatment. Thus, a typical refill would involve two screenings.

person-years at risk:

This is a statistical concept, and refers to the total time at risk in a defined time period for a defined group of individuals. Thus, if one individual is at risk for 5 years, a total of 5 person-years is accumulated. Similarly, if 10 people are at risk for two years, and 20 people are at risk for 5 years, a total of 120 person-years is accumulated. If deaths are expressed relative to this denominator, the observed number will have a Poisson distribution, provided that the hazard rate remains constant (or approximately so) for that group during the defined time interval.

age at risk:

In a cohort study an individual is followed from some initial event (e.g. radiation exposure) until the end of the study, or until that individual is lost to contact or has died. During this period of follow-up the individual's age will change, and it is necessary to classify both observed number of deaths and person-years at risk by the current age of each individual in each particular year. This age is referred to as "age at risk".

calendar year at risk:

In an analogous fashion, to classify person-years at risk and observed number of deaths by age at risk it may be necessary to also classify these two variables by the particular calendar year under consideration. This is referred to as the "calendar year at risk".

observed number of deaths:

The number of deaths attributable to a specific cause or group of causes occurring amongst a group of individuals during a defined time period.

expected number of deaths:

The number of deaths from that specific cause or group of causes which would have been expected to occur amongst the group if they had experienced the hazard rate (death rate) from some comparison group (usually the population), appropriately adjusted for any factors which may differ between the population and the special group under study such as sex or age which affect the death rate.

Standardized Mortality Ratio (SMR):

The ratio of observed to expected deaths in a particular group or cohort of individuals. If the expected numbers are derived from a large population, the SMR is the maximum likelihood estimate of the relative risk of death for that group compared to the population.

output:

The energy, expressed in kerma in air, produced per unit of time by a fluoroscope in operation.

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